## REMARKS

In the Final Action dated September 29, 2003, Claims 1-18 and 24-35 are pending and under consideration. Claims 1, 3-5, 24-28, 33 and 35 are rejected under 35 U.S.C. 102(b) as allegedly anticipated by Kimura et al. (U.S. Patent 4,862,358). Claim 2 is rejected under 35.U.S.C. §103 based on Kimura et al. in view of Kamb (U.S. Patent 5,869,242). Claims 6-7 and 29-30 are rejected under 35.U.S.C. §103 based on Kimura et al. in view of Sutherland et al. (U.S. Patent 5,985,619). Claims 10, 14, and 34 are rejected under 35.U.S.C. §103 based on Kimura et al. in view of Koster (U.S. Patent 6,074,823). Claims 8-9, 11-13 and 31-32 are rejected under 35.U.S.C. §103 based on Kimura et al. in view of Caprioli (U.S. Patent 5,808,300). Claim 16 is rejected under 35.U.S.C. §103 based on Kimura et al. in view of Koster and Sutherland et al. Claim 15 is rejected under 35.U.S.C. §103 based on Kimura et al. in view of Caprioli and further in view of Sutherland et al. Claims 17-18 are rejected under 35.U.S.C. §103 based on Kimura et al. in view of Koster and further in view of Caprioli.

This Response addresses each of the Examiner's rejections. Applicants therefore respectfully submit that the present application is in condition for allowance or at least in better condition for appeal. Favorable consideration of all pending claims is therefore respectfully requested.

In respect to the §102(b) rejection based on Kimura et al., Applicants observe that Kimura et al. teach a signal processing method in autoradiography for determining the base sequence of DNA or DNA fragments. The method employs at least four groups of base-specific cleavage products (G,A,T,C, respectively), which are resolved in one dimensional directions and in parallel relative to each other on a support medium, and generates digital image data corresponding to the autoradiograph.

On the other hand, the present claims are directed to methods of detecting a difference of one or more nucleotides between a nucleic acid molecule to be tested and a reference nucleic acid molecule, by subjecting the test nucleic acid molecule to single-base specific cleavage to generate oligonucleotide fragments; separating the fragments by MALDI-TOF MS or other equivalent procedures to produce a fingerprint of the fragments; and identifying an altered peak in the fingerprint relative to the reference nucleic acid molecule.

The Examiner contends that the methods disclosed by Kimura et al. employ single base-specific cleavage. The Examiner states that the rejection is based on the fact that any process, such as electrophoresis as used by Kimura et al., which is able to produce a fingerprint of the oligonucleotide fragments comprising one or more peaks wherein a peak represents the mass of each fragment, is equivalent to MALDI-TOF MS.

Applicants respectfully submit that as described in the specification at page 3, lines 11-13, "MALDI-TOF MS" stands for matrix assisted laser desorption ionization – time of flight mass spectrometer. A MALDI-TOF MS procedure has the ability to accurately determine the mass of biomolecules of a limited size. Those skilled in the art would easily recognize the distinctions between a MALDI-TOF MS procedure and a conventional gel electrophoresis. equivalents thereof that are attributable to the efficacies of the claimed methods. Furthermore, as described in the specification at page 3, lines 21-24, the methods of the present invention, which exploit the accuracy of mass determination of MALDI-TOF MS and are applicable to large DNA fragments, do not require gel electrophoresis.

However, in an effort to favorably advance the prosecution of the present application, Applicants have amended the claims to delete the term " or other equivalent procedures" from

independent claims 1, 10, 24, 33 and 35. Kimura et al. do not teach or suggest a procedure even remotely related to a MALDI-TOF MS procedure.

Applicants further respectfully submit that the method taught by Kimura et al. is essentially for the purpose of determining the sequence of a nucleic acid molecule, not for detecting one or more mutations. Kimura et al. do not teach or suggest identifying by MALDI-TOF MS, an altered peak relative to a reference nucleic acid molecule. The Examiner has pointed to col. 21, lines 33-43 of Kimura et al. for the alleged teaching of identification of an altered peak relative to a reference nucleic acid molecule. However, the indicated portion of the text in the Kimura et al. patent only teaches comparing one group of base-specific cleavage products (e.g., cleavage of all A's) of a test nucleic acid molecule with a reference mixture of all base cleavage products (i.e., cleavage of A's, C's, G's and T's of the same molecule) in order to determine the sequence of the test molecule. Kimura et al do not teach identifying an altered peak relative to a reference molecule to identify the differences between the test molecule and the reference molecule for the purpose of detecting one or more mutations.

Accordingly, it is respectfully submitted that Kimura et al. do not teach the claimed invention. Withdrawal of the rejection of claims 1, 3-5, 24-28, 33 and 35 under 35 U.S.C. §102(b) as allegedly anticipated by Kimura et al. is therefore respectfully requested.

Claim 2 is rejected under 35.U.S.C. §103 based on Kimura et al. in view of Kamb (U.S. Patent 5,869,242).

The Examiner admits that Kimura et al. do not teach a method, wherein the nucleic acid molecule to be tested is amplified by a PCR prior to base specific cleavage. However, the Examiner argues that Kamb teaches a method, wherein the nucleic acid molecule to be tested is amplified by a PCR prior to base specific cleavage.

As submitted above, Kimura et al. do not teach or suggest a method of detecting the differences between a test molecule and a reference molecule by subjecting the test molecule to single-base-specific cleavage and separating the resulting cleavage products based on mass by MALDI-TOF MS, as presently claimed. This deficiency of Kimura et al. is not cured by Kamb. Specifically, Kamb does not teach or suggest a method which invovles subjecting the test nucleic acid molecule to single-base-specific cleavage. Applicants respectfully submit that the references, taken alone or in combination, do not teach or suggest the claimed methods. As such, the rejection of claim 2 under §103 based on the combination of Kimura et al. and Kamb is overcome. Withdrawal of the rejection is therefore respectfully requested.

Claims 6-7 and 29-30 are rejected under 35.U.S.C. §103 based on Kimura et al. in view of Sutherland et al. (U.S. Patent 5,985,619).

The Examiner admits that Kimura et al. does not teach the method wherein the base specific cleavage is uracil specific and mediated by uracil-N-glycosylase. However, the Examiner argues that Sutherland et al. teach the method wherein the base specific cleavage is uracil specific and mediated by uracil-N-glycosylase.

Applicants reassert that Kimura et al. do not teach or suggest a method of detecting the differences between a test molecule and a reference molecule by subjecting the test molecule to single-base-specific cleavage and separating the resulting cleavage products based on mass by MALDI-TOF MS, as presently claimed. This deficiency of Kimura et al. is not cured by Sutherland et al.

Furthermore, Applicants respectfully submit that Sutherland et al. merely teach the availability of uracil-N-glycosylase as a uracil-specific cleavage enzyme. Sutherland et al. do not provide any teaching or suggestion for those skilled in the art to use uracil and uracil-N-

glycosylase in a method of detecting nucleotide differences, let alone in a method detecting nucleotide differences which employs MALDI-TOF MS.

The Examiner has identified certain "express advantages" of Sutherland et al. Applicants are presently unaware of the relevance of the alleged advantages. Assuming, pro arguendo, the existence and relevance of such advantages, Applicants submit that these advantages alone provide no motivation for those skilled in the art to modify the method disclosed by Kimura et al. In this regard, Applicants submit that the suggestion or teaching to combine the references must be found in the prior art, not in applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Accordingly, it is respectfully submitted that the rejection of claims 6-7 and 29-30 under 35 U.S.C. §103 (a) based on the combination of Kimura et al. and Sutherland et al. is improper. Withdrawal of the rejection is therefore respectfully requested.

Claims 10, 14, and 34 are rejected under 35.U.S.C. §103 based on Kimura et al. in view of Koster (U.S. Patent 6,074,823).

The Examiner admits that Kimura et al. do not teach a method of using a computer capable of controlling a method of detecting mutation by MALDI-TOF MS. However, the Examiner contends that Koster teaches the method of using a computer capable of controlling a method of detecting mutation by MALDI-TOF MS (column 5, lines 22-35). Thus, the Examiner concludes that one skilled in the art would have combined and substituted a computer capable of controlling a method of detecting mutation by MALDI-TOF MS of Koster into the mass spectrometry to assess DNA sequence polymorphisms of Kimura et al. in order to improve the sequencing of nucleic acids by automated procedures.

Applicants respectfully submit that Kimura et al. do not teach or suggest a method of detecting the differences between a test molecule and a reference molecule by subjecting the test molecule to single-base-specific cleavage, as presently claimed. The mere fact that Koster teaches a computer program that makes a detection procedure automated does not cure the deficiency of Kimura et al.

Applicants respectfully submit that Kimura et al. and Koster, taken alone or in combination, do not teach or suggest the claimed methods. As such, the rejection of claims 10, 14, and 34 under §103 based on the combination of Kimura et al. and Koster is overcome. Withdrawal of the rejection is therefore respectfully requested.

Claims 8-9, 11-13 and 31-32 are rejected under 35.U.S.C. §103 based on Kimura et al. in view of Caprioli (U.S. Patent 5,808,300).

The Examiner admits that Kimura et al. do not teach the method of subjecting fragmentation products to further separation by the post source decay method. However, the Examiner argues that Caprioli teaches the method of subjecting fragmentation products to further separation by post source decay method (Column 3, lines 9-11).

Applicants respectfully submit that Kimura et al. do not teach or suggest a method of detecting the differences between a test molecule and a reference molecule by subjecting the test molecule to single-base-specific cleavage and separating the resulting cleavage products based on mass by MALDI-TOF MS, as presently claimed. The mere fact that Caprioli teaches subjecting cleavage products to further separation by post source decay does not cure the deficiency of Kimura et al. Therefore, Applicants respectfully submit that Kimura et al. and Caprioli, taken alone or in combination, do not teach or suggest the claimed methods. As such,

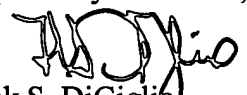
the rejection of claims 8-9, 11-13 and 31-32 under §103 based on the combination of Kimura et al. and Caprioli is overcome. Withdrawal of the rejection is therefore respectfully requested.

As further set forth in the Final Action, the Examiner has rejected certain dependent claims based on combinations of Kimura et al. and two other references. Specifically, claim 16 is rejected under 35.U.S.C. §103 based on Kimura et al. in view of Koster and Sutherland et al. Claim 15 is rejected under 35.U.S.C. §103 based on Kimura et al. in view of Caprioli and further in view of Sutherland et al. Claims 17-18 are rejected under 35.U.S.C. §103 based on Kimura et al. in view of Koster and further in view of Caprioli.

Applicants respectfully submit that the primary reference to Kimura et al. does not teach or suggest a method of detecting the differences between a test molecule and a reference molecule by subjecting the test molecule to single-base-specific cleavage and separating the resulting cleavage products based on mass by MALDI-TOF MS, as presently claimed. The secondary references, Sutherland et al., Koster and Caprioli, alone or in combination, do not cure the deficiency of the primary reference to Kimura et al. Therefore, the above rejections of claims 15, 16, and 17-18 under §103 based on Kimura et al. as the primary reference are overcome. Withdrawal of these rejections is therefore respectfully requested.

In view of the foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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